Phytochemistry and Pharmacology of *Berberis* Species

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ABSTRACT

The genus *Berberis* (Berberidaceae) includes about 500 species worldwide, some of which are widely cultivated in the north-eastern regions of Iran. This genus consists of spiny deciduous evergreen shrubs, characterized by yellow wood and flowers. The cultivation of seedless barberry in South Khorasan goes back to two hundred years ago. Medicinal properties for all parts of these plants have been reported, including: Antimicrobial, antiemetic, antipyretic, antioxidant, anti-inflammatory, anti-arrhythmic, sedative, anti-cholinergic, cholagogic, anti-leishmaniasis, and anti-malaria. The main compounds found in various species of *Berberis*, are berberine and berbamine. Phytochemical analysis of various species of this genus revealed the presence of alkaloids, tannins, phenolic compounds, sterols and triterpenes. Although there are some review articles on *Berberis vulgaris* (as the most applied species), there is no review on the phytochemical and pharmacological activities of other well-known species of the genus *Berberis.* For this reason, the present review mainly focused on the diverse secondary metabolites of various species of this genus and the considerable pharmacological and biological activities together with a concise story of the botany and cultivation.

Key words: *Berberis*, pharmacological effects, phytochemistry, zereshk

INTRODUCTION

The genus *Berberis* (Berberidaceae) includes about 500 species that commonly occur in most areas of central and southern Europe, the northeastern region of the United States and in South Asia including the northern area of Pakistan.[1,2] There are five species of this plant in Iran, two of them (*B. orthobotrys* and *B. khorassanica)* exclusively growing in the northern, eastern, and south eastern highlands of Iran (Alborz, Qaradagh in Azerbaijan, Mountains of Khorasan, Barez Mountain in Kerman).[3,4]

Berberis species, called "zereshk" in Persian language, are widely cultivated in Iran. The South-Khorasan province (especially around Birjand and Qaen) is the major field of cultivation for zereshk in the world.[5] Medicinal properties for all parts of these plants have been reported [Table 1], including tonic, antimicrobial, antiemetic, anti-pyretic, anti-pruritic, antioxidant, anti-inflammatory, hypotensive, anti-arrhythmic, sedative, anti-nociceptive, anti-cholinergic, cholagogic, and have been employed in cholecystitis, cholelithiasis, jaundice, dysentery, leishmaniasis, malaria, gall stones, hypertension, ischemic heart diseases (IHDS), cardiac arrhythmias and cardiomyopathies.[2-6] Also, barberry has been used to treat diarrhea, reduce fever, improve appetite, and relieve upset stomach.[7]

Among the several species of this genus, *Berberis vulgaris* is well known and its fruits have been used in the preparation of a special dish with rice and also in *Berberis* juice.[8-10] Sometimes it has been used as a tea made from the bark of the plant.[7] Besides nutritional consumption, various parts of this plant including roots, bark, leaves and fruits have been employed in folk and traditional medicine for a long time in Iran.[7] The stem and root barks are used for their cathartic, diuretic, febrifuge, anti-bilious, and antiseptic properties. Also, the decoction of leaves is used as anti-scorbutic in dysentery, scurvy angina, and sore throat.[11] This article reviews mainly the phytochemical compounds of various species of *Berberis* together with the highlighted pharmacological and biological properties.

Plant characteristics

The *Berberis* genus consists of spiny deciduous evergreen shrubs, characterized by yellow wood and flowers,[9] dimorphic and long shoots together with the short ones (1-2 mm). The leaves on long shoots are not involved in photosynthesis but develop into three-spine thorns and finally short shoots with several leaves

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Table 1: Pharmacological and biological activity of the various species of Berberis genus

Plant name	Pharmacological/biological effect	Reference
B. vulgaris	Antihistaminic, anticholinergic, anti-inflammatory and anti-nociceptive effects	(16)
B. croatica	Antimicrobial activity	(10)
B. aristata	Cytotoxic activity, anticancer activity, laxative and useful in rheumatism; hypoglycemic activity, anti-osteoporotic activity	(17-19)
B. koreana	Cytotoxic activity	(20)
B. aetnensis	The plants is useful in rheumatic complaints and other types of chronic inflammations and antimicrobial activity	(21)
B. heterophylla	Antimicrobial activity	(22)
B. umbellate	Useful in treatment of cholera, acute diarrhea, amoebiasis and latent malaria	(23)
B. lyceum	Useful in treatment of eye diseases, liver and heart diseases, antihistaminic activity, stomachic, astringent, antipyretic and diaphoretic properties, anti-hyperglycemic effects	(24)
B. aquifolium	Antibacterial activity	(25)
B. repens	Antibacterial activity	(25)
B.integerrima	Antibacterial activity	(26)
B. hispanica	Increase of antibody production, immunosuppressive	(27)
B. thunbergii	Antimicrobial activity	(28)

Table 2: The main isolated compounds reported from different species of berberis. Structures of the compounds below are shown in Figure 1

Compound name	Plant source
Lupeol	*B. vulgaris*
Oleanolic acid	*B. vulgaris*
Stigmasterol	*B. vulgaris*
Stigmasterolglucoside	*B. vulgaris*
Berberamine	*B. vulgaris*
Palmatine	*B. vulgaris*
Berberine	*B. vulgaris*
Oxyberberine	*B. vulgaris*
Columbamine	*B. vulgaris*
Isocorydine	*B. vulgaris*
Lambertine	*B. vulgaris*
Magniflorine	*B. vulgaris*
Oxycanthine	*B. vulgaris*
N-(p-trans-Coumaroyl) tyramine	*B. vulgaris*
cannabisin G	*B. vulgaris*
(±)-lyoniresinol	*B. vulgaris*
2,5-bis-(2'-methoxy-5'-methylphenyl)-furan	*B. umbellata*
1,4-bis-(2'-hydroxy-5'-methylphenyl)-butan-l: Cdione	*B. umbellata*

contd...

Table 2: The main isolated compounds reported from different species of berberis. Structures of the compounds below are shown in Figure 1

Compound name	Plant source
Berbamine	*B. aristata*
(+)-N-methylcoclaurine	*B. montana*
(-)-pronuciferine	*B. montana*
(+)-9-hydroxynuciferine	*B. montana*
(+)-orientine	*B. montana*
2-norberbamunine	*B. stoloniferais*
Berbamunine	*B. stoloniferais*
Aromoline	*B. stoloniferais*
Isotetrandrine	*B. stoloniferais*
23-trans-p-coumaroyloxy- 2a, 3a-dihydroxyolean-12-en-28-oic acid	*B. koreana*
23-cis-p-coumaroyloxy-2a, 3a-dihydroxyolean-12-en-28-oic acid	*B. koreana*
5'-methoxyhydnocarpin-D	*B. aquifolium* *B. fremontii* *B. repens*
Pheophorbide- a	*B. aquifolium* *B. fremontii* *B. repens*
Jatrorrhizine	*B. umbellate*

(1-10 cm long, simple, and either entire, or with spiny margins) involved in photosynthesis. Many deciduous species such as *B. thunbergii* and *B. vulgaris* indicate pink or red autumn color, while the leaves are brilliant white beneath in some Chinese evergreen species (*B. candidula* and *B. verruculosa*), and dark red to violet foliage is found in horticultural variants of *B. thunbergii*. On a single flower-head, the flowers are appears alone or in racemes. They are yellow or orange, 3-6 mm long, with both six sepals and petals (usually with similar color) in alternating whorls. The *Berberis'* fruits are small berries (5-15 mm) which turn red or blue after ripening.[12,13]

In the lifecycle of *Berberis*, there are sexual and asexual reproduction processes which enable the plant to survive in harsh conditions. The distinctive yellow flowers of these plants appear in clusters and hang downwards from the stem. The reproductive organs of the flower are protected from rain by three inner concave sepals as well as six petals that completely enclose the stamens and anthers.[14]

The land under cultivation

Cultivation of zereshk in Iran is limited to the South-Khorasan province, especially around Birjand and Qaen. About 72% of the production is in Qaen and about 32% in Birjand. According to evidence the cultivation of seedless barberry in South-Khorasan goes back to two hundred years ago. The export of *Berberis* fruits is not considerable, because appropriate packaging is not available which affects the appearance and color of barberries. Besides this problem, barberry is not so familiar to people outside Iran.[15]

Pharmacological and biological effects

So far, many pharmacological and biological effects of various species of *Berberis* have been reported, some of which are summarized below in Table 1.

Phytochemistry

The main compounds, found in various species of *Berberis*, [Table 2] are berberine and berbamine [Figure 1]. Phytochemical analysis of the crude extract of *B. vulgaris* revealed the presence of alkaloids, tannins and phenolic compounds.[2] The triterpenes: lupeol (1), separated from its fruits, and oleanolic acid (2), isolated from ethanolic extract; the sterol: stigmasterol (3), obtained from hexane extract, and stigmasterol glucoside (4), from ethyl acetate extract; the alkaloids: berberamine (5), palmatine and (6) berberine (7), were reported for the first time from *B. vulgaris*.[11] Other important alkaloids: oxyberberine (8), columbamine

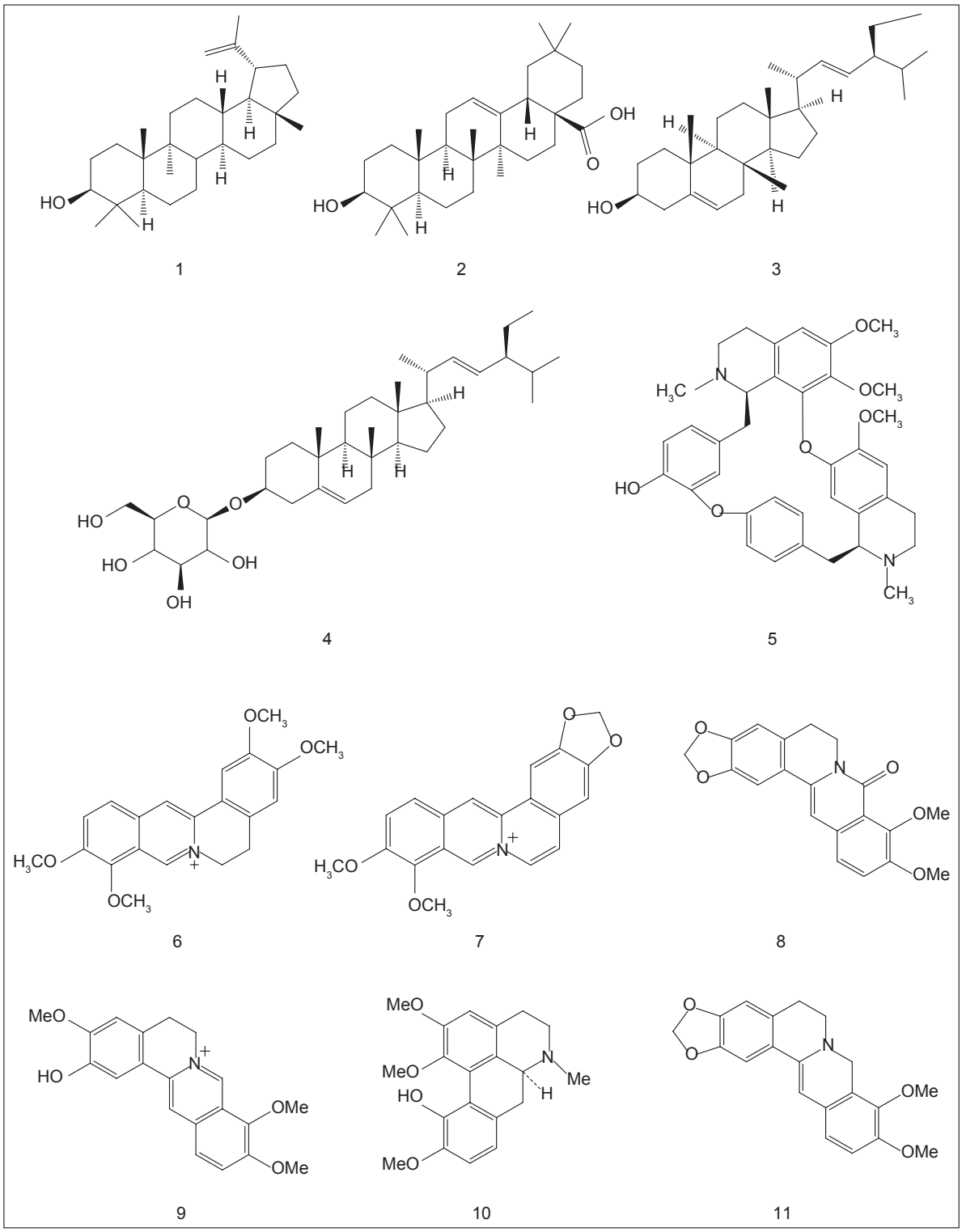
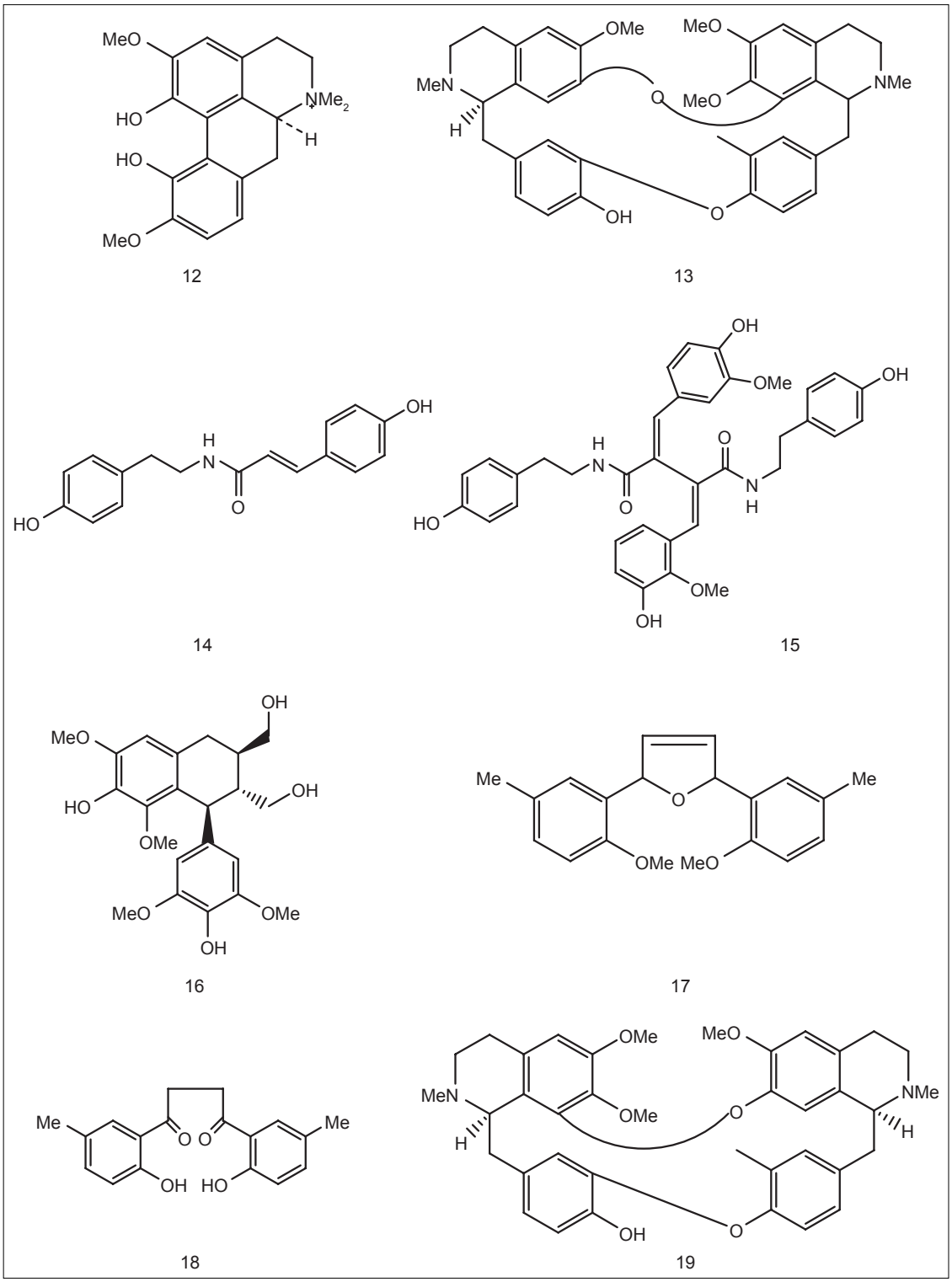


Figure 1: The structures of some phytochemical compounds isolated from various species of *Berberis*



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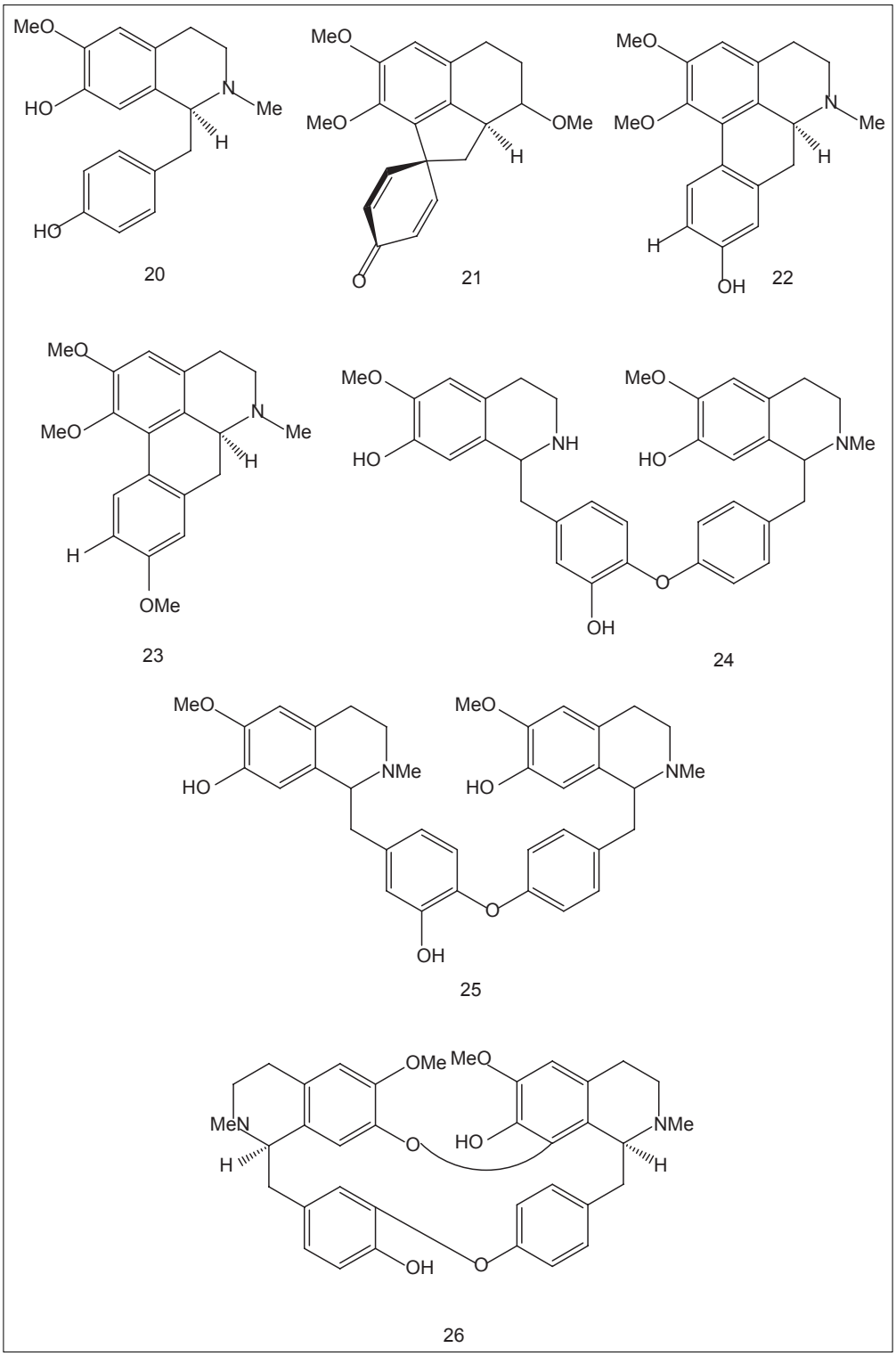
(9), isocorydine (10), lambertine (11), magniflorine (12) and bisbenzlisoquinolines *e.g.,* oxycanthine (13)[7] have been reported from this plant. Cytoprotective compounds including N-(*p-trans*-coumaroyl) tyramine (14), cannabisin G (15), and (±)-lyoniresinol (16)[29] have been isolated from ethyl acetate extract of *B. vulgaris* [Figure 1]. The compounds: 2,5-bis-(2'-methoxy-5'-methylphenyl)-furan (17) and 1,4-bis-(2'-hydroxy-5'-methylphenyl)-butan-l: cdione (18) were isolated and identified from the ethanolic extract of *B. umbellate* roots [Figure 1].[30-34] Chromatographic separation of the crude alkaloid fraction of *B. chitria* afforded a new aporphine (isoquinoline) alkaloid as an amorphous solid



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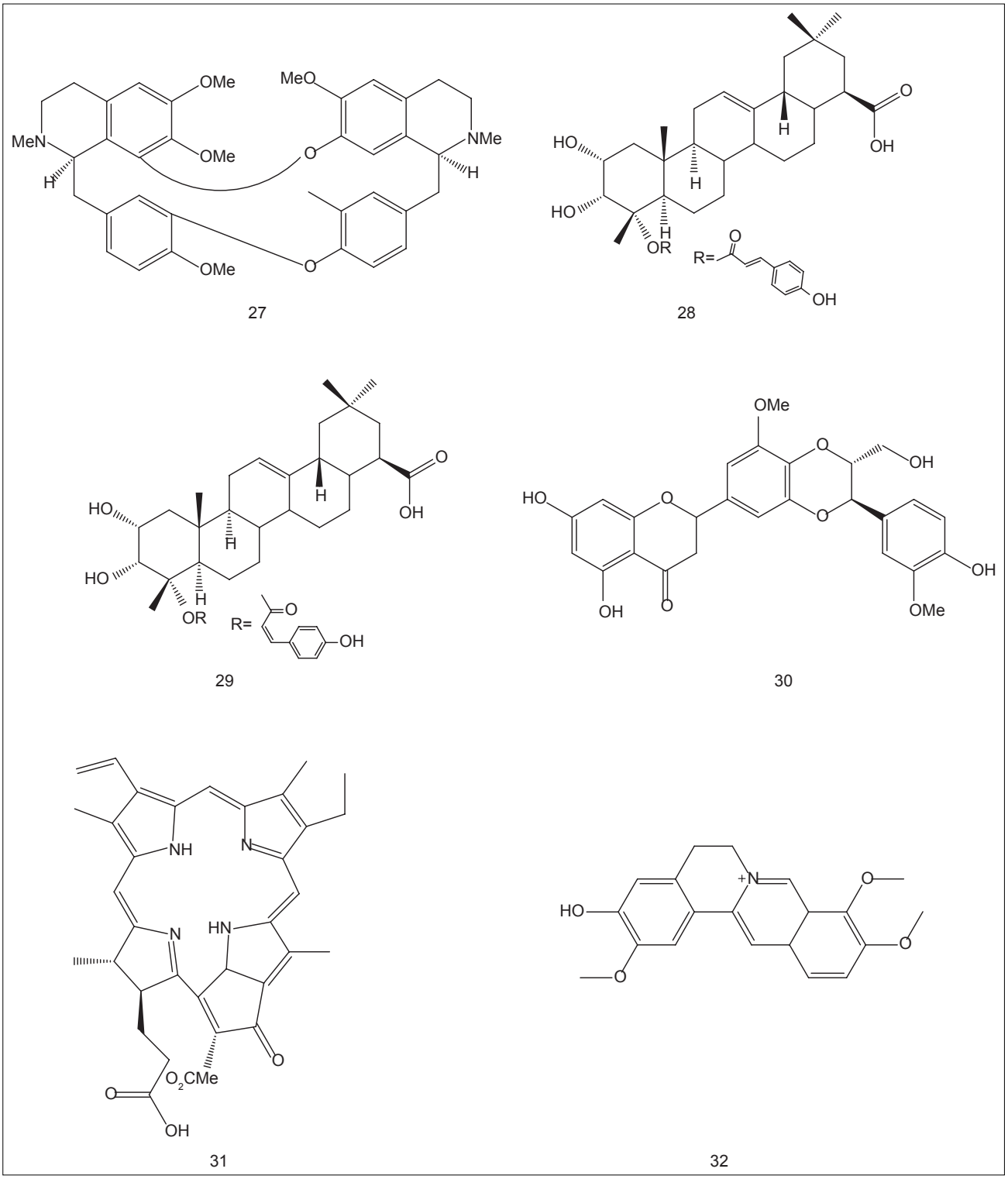
named: O-methylcorydine-N-oxide.[31] *B. aristata* contains also a valuable isoquinoline alkaloid berbamine (19).[17]

B. montana contained four monomeric isoquinoline alkaloids: The benzyl isoquinoline (+)-N-methylcoclaurine (20), the proaporphine (-)-pronuciferine (21), and the aporphines (+)-9-hydroxynuciferine (22) and (+)-orientine (23), all of which were separated from methanol extract of this plant [Figure 1].[32] *B. stolonifera* is another species of *Berberis* which was investigated for biosynthetic pathway, and resulted in isolation of five bis-benzyl isoquinoline alkaloids from dried callus and suspension cultures as: 2-norberbamunine (24), berbamunine

(25), and aromoline (26), berbamine (19) and isotetrandrine (27) [Figure 1].[33]

Several triterpenoids such as 23-*trans-p*-coumaroyloxy- 2a, 3a-dihydroxyolean-12-en-28-oic acid (28) and 23-*cis-p*-coumaroyloxy-2a, 3a-dihydroxyolean-12-en-28-oic acid (29) were isolated and structurally elucidated from *B. korean* [Figure 1].[20]

The active inhibitors 5'-methoxyhydnocarpin-D (30) and pheophorbide- a (31) have been isolated from the leaves of *B. aquifolium*, *B. fremontii* and *B. repens* respectively.[25] Furthermore,



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Jatrorrhizine (32) as aporotoberberine alkaloid has been separated from *B. umbellate*.[23] Tetrahydro isoquinoline alkaloids are another noteworthy alkaloid group reported from *B. tinctoria*.

CONCLUSIONS

Crocus sativus, *Cuminum cyminum* and *Berberis vulgaris* are important medicinal food plants growing widely in Iran and also cultivated for their nutritional purposes and economic significance.[35,36] "Zereshk" is a Persian common name for the genus *Berberis* that has been frequently consumed as a food additive and also traditionally as a remedy in Iran. In traditional and folklore medicine, it has been used for its many pharmacological and biological activities, which make it an effective remedy for various kinds of illnesses. The literature reviews revealed the presence of quinoline and isoquinoline alkaloids together with sterols and triterpenes. Bereberine and other similar alkaloids have been identified as the main responsible natural compounds for diverse medicinal properties.

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